(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 October 2004 (14.10.2004)

PCT

(10) International Publication Number
WO 2004/087683 A1

(51) International Patent Classification[7]: C07D 261/16, A61K 31/42

(21) International Application Number: PCT/IN2003/000139

(22) International Filing Date: 4 April 2003 (04.04.2003)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/087683 A1

(54) Title: NOVEL CRYSTALLINE FORMS OF VALDECOXIB

(57) Abstract: The present invention relates to novel crystalline forms of valdecoxib, to processes for their preparation and to pharmaceutical compositions containing them.

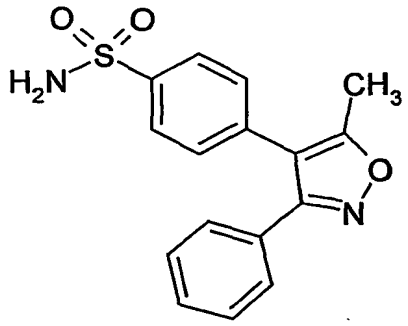
NOVEL CRYSTALLINE FORMS OF VALDECOXIB

FIELD OF THE INVENTION

The present invention relates to novel crystalline forms of valdecoxib, to processes for their preparation and to pharmaceutical compositions containing them.

BACKGROUND OF THE INVENTION

Valdecoxib of formula (1):



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or 4-(5-Methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide is a highly selective and potent cyclooxygenase-2 inhibitor in human whole blood and useful for the treatment of arthritis and pain. The therapeutic uses of valdecoxib are disclosed in WO 9625405.

Two crystalline forms of valdecoxib, form A and form B, are mentioned in WO 9806708.

We have discovered three stable novel crystalline forms of valdecoxib and these forms are found to be suitable for pharmaceutical preparations.

The object of the present invention is to provide stable novel crystalline forms of valdecoxib, processes for preparing these forms and pharmaceutical compositions containing them.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of valdecoxib, designated as form I, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 9.7, 13.1, 14.0, 14.5, 17.0, 17.1, 17.7, 19.4, 20.9, 21.3, 21.8, 24.1, 25.4, 26.3 and 29.1 degrees. Figure 1 shows typical form I x-ray powder diffraction pattern.

In accordance with the present invention, a process is provided for preparation of valdecoxib form I. In this process, valdecoxib is dissolved in dimethyl formamide or N,N-dimethyl acetamide and valdecoxib form I is isolated from the solution. Valdecoxib in any crystalline form may be used. If valdecoxib form I is used in the process, its serves as a method of purification of valdecoxib form I. A mixture of dimethyl formamide and N,N-dimethyl acetamide; or dimethyl formamide or N,N-dimethyl acetamide mixed with any other solvent may be used. Valdecoxib form I can be isolated by the techniques like cooling, partial removal of the solvent or combination thereof. Crystallization may be initiated with the aid of seed crystals. Preferably, valdecoxib is mixed with dimethyl formamide or N,N-dimethyl acetamide and heated to about 50°C to reflux temperature. The solution so formed is preferably maintained at 25°C to 30°C for 3 to 5 hours and the valdecoxib form I crystals formed are separated by filtration or centrifugation.

In accordance with the present invention, there is provided a novel crystalline form of valdecoxib, designated as form II, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 12.2, 15.4, 15.9, 19.9, 20.6, 22.0, 23.0, 23.6, 23.9, 24.5, 25.1, 28.6 and 31.3 degrees. Figure 2 shows typical form II x-ray powder diffraction pattern.

In accordance with the present invention, a process is provided for preparation of valdecoxib form II. In this process, valdecoxib is dissolved in acetonitrile and isolated valdecoxib form II from the solution. Valdecoxib in any crystalline form may be used. Preferably valdecoxib is dissolved in acetonitrile at about 40°C to 45°C and valdecoxib form II is separated at about 25°C - 30°C. The valdecoxib form II may be collected by filtration or centrifugation.

In accordance with the present invention, there is provided a novel crystalline form of valdecoxib, designated as form III, characterized by an x-ray

powder diffraction pattern having peaks expressed as 2θ at about 11.6, 12.2, 12.9, 13.3, 15.4, 15.7, 16.7, 17.0, 17.4, 18.1, 19.7, 20.6, 21.9, 22.4, 23.1, 23.4, 23.8, 24.4, 25.3, 25.7, 26.1, 28.5 and 29.7 degrees. Figure 3 shows typical form III x-ray powder diffraction pattern.

In accordance with the present invention, a process is provided for preparation of valdecoxib form III. In this process, valdecoxib is dissolved in an ester solvent and isolated valdecoxib form III from the solution. Preferably the solution is cooled to 5^0C to 30^0C to get the crystals of valdecoxib form III. The valdecoxib form III may be collected by filtration or centrifugation. Valdecoxib in any crystalline form may be used in the process. The suitable ester solvent is selected from n-butyl acetate, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl acetate, ethyl formate, methyl formate. A combination of the ester solvents may also be used.

In accordance with the present invention, there is provided a pharmaceutical composition comprising form I of valdecoxib and a pharmaceutically acceptable carrier or diluent.

In accordance with the present invention, there is provided a pharmaceutical composition comprising form II of valdecoxib and a pharmaceutically acceptable carrier or diluent.

In accordance with the present invention, there is provided a pharmaceutical composition comprising form III of valdecoxib and a pharmaceutically acceptable carrier or diluent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a x-ray powder diffraction spectrum of valdecoxib form I.

Figure 2 is a x-ray powder diffraction spectrum of valdecoxib form II.

Figure 3 is a x-ray powder diffraction spectrum of valdecoxib form III.

x-Ray powder diffraction spectrum was measured on a Siemens D5000 x-ray powder diffractometer having a copper-Kα radiation.

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitations on the scope of spirit of the invention.

Example 1

Valdecoxib (10 gm, obtained by the process described in example 1 of WO 9625405) is dissolved in dimethyl formamide (50 ml), heated to 50°C and the solution obtained is cooled to 25°C and maintained at 25°C to 30°C for 3 hours. The separated crystals are filtered to give 9 gm of valdecoxib form I.

Example 2

Valdecoxib (10 gm) is dissolved in acetonitrile (125 ml), heated to 40°C and the solution obtained is cooled to 25°C and maintained at 25°C to 30°C for 6 hours. The separated crystals are filtered to give 9.5 gm of valdecoxib form II.

Example 3

Example 1 is repeated using valdecoxib form II for valdecoxib to give valdecoxib form I.

Example 4

Example 2 is repeated using valdecoxib form I for valdecoxib to give valdecoxib form II.

Example 5

Valdecoxib (10 gm) is mixed with n-butyl acetate (100 ml), heated to 80°C. The solution so formed is cooled to 25°C and maintained at about 25°C for 5 hours. The separated crystals are filtered to give 8.5 gm of valdecoxib form III.

Example 6

Example 5 is repeated using valdecoxib form II for valdecoxib to give valdecoxib form III.

We claim:

1. A crystalline valdecoxib form I, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 9.7, 13.1, 14.0, 14.5, 17.0, 17.1, 17.7, 19.4, 20.9, 21.3, 21.8, 24.1, 25.4, 26.3 and 29.1 degrees.
2. A crystalline valdecoxib form I as defined in claim 1, further characterized by an x-ray powder diffraction pattern as in figure 1.
3. A process for preparation of valdecoxib form I as defined in claim 1, which comprises the steps of: a) dissolving valdecoxib in dimethyl formamide or N,N-dimethyl acetamide; and b) isolating valdecoxib form I from the solution.
4. A process according to claim 3, wherein valdecoxib is dissolved in dimethyl formamide.
5. A process according to claim 3, wherein the solution formed in (a) is cooled to 25°C to 30°C and the separated crystals are collected by filtration or centrifugation.
6. A crystalline valdecoxib form II, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 12.2, 15.4, 15.9, 19.9, 20.6, 22.0, 23.0, 23.6, 23.9, 24.5, 25.1, 28.6 and 31.3 degrees.
7. A crystalline valdecoxib form II as defined in claim 6, further characterized by an x-ray powder diffraction pattern as in figure 2.
8. A process for preparation of valdecoxib form II as defined in claim 6, which comprises:

a) dissolving valdecoxib in acetonitrile; and
b) isolating valdecoxib form II from the solution formed in (a).

9. A process according claim 8, wherein valdecoxib form II is isolated from the solution at about 25°C to 30°C.
10. A crystalline valdecoxib form III, characterized by an x-ray powder diffraction pattern having peaks expressed as 2θ at about 11.6, 12.2, 12.9, 13.3, 15.4, 15.7, 16.7, 17.0, 17.4, 18.1, 19.7, 20.6, 21.9, 22.4, 23.1, 23.4, 23.8, 24.4, 25.3, 25.7, 26.1, 28.5 and 29.7 degrees.
11. A crystalline valdecoxib form III as defined in claim 10, further characterized by an x-ray powder diffraction pattern as in figure 3.
12. A process for preparation of valdecoxib form III as defined in claim 10, which comprises:

a) dissolving valdecoxib in an ester solvent; and

b) isolating valdecoxib form III from the solution formed in (a).

wherein the ester solvent is selected from n-butyl acetate, ethyl acetate, methyl acetate, isopropyl acetate, tert-butyl acetate, ethyl formate and methyl formate.

13. A process according to claim 12, wherein the ester solvent is n-butyl acetate.

14. A process according to claim 13, wherein valdecoxib form III is isolated at 25^0C to 30^0C.

15. A pharmaceutical composition comprising valdecoxib form I of claim 1 and a pharmaceutically acceptable carrier or diluent.

16. A pharmaceutical composition comprising valdecoxib form II of claim 6 and a pharmaceutically acceptable carrier or diluent.

17. A pharmaceutical composition comprising valdecoxib form III of claim 10 and a pharmaceutically acceptable carrier or diluent.

fig. 1/3

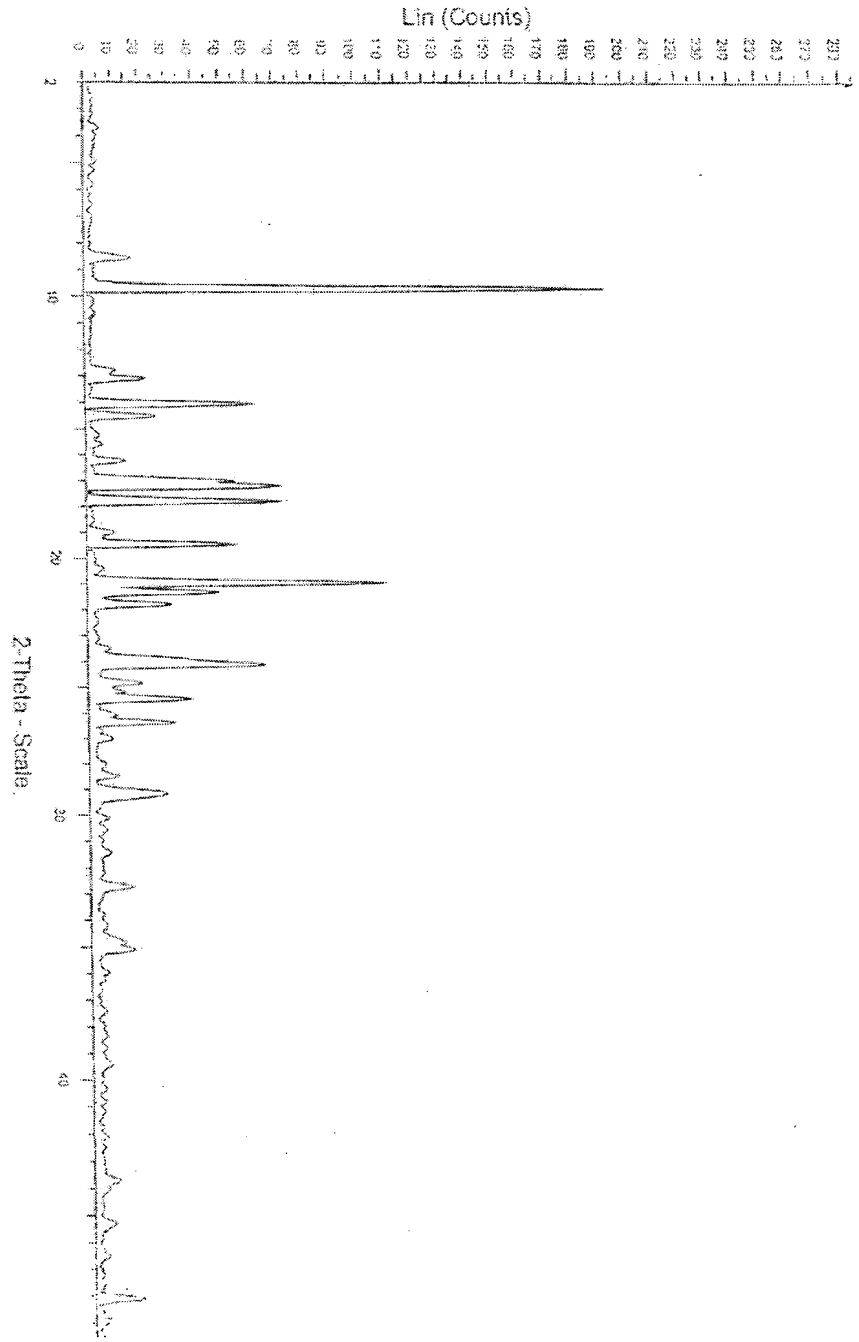


fig. 2/3

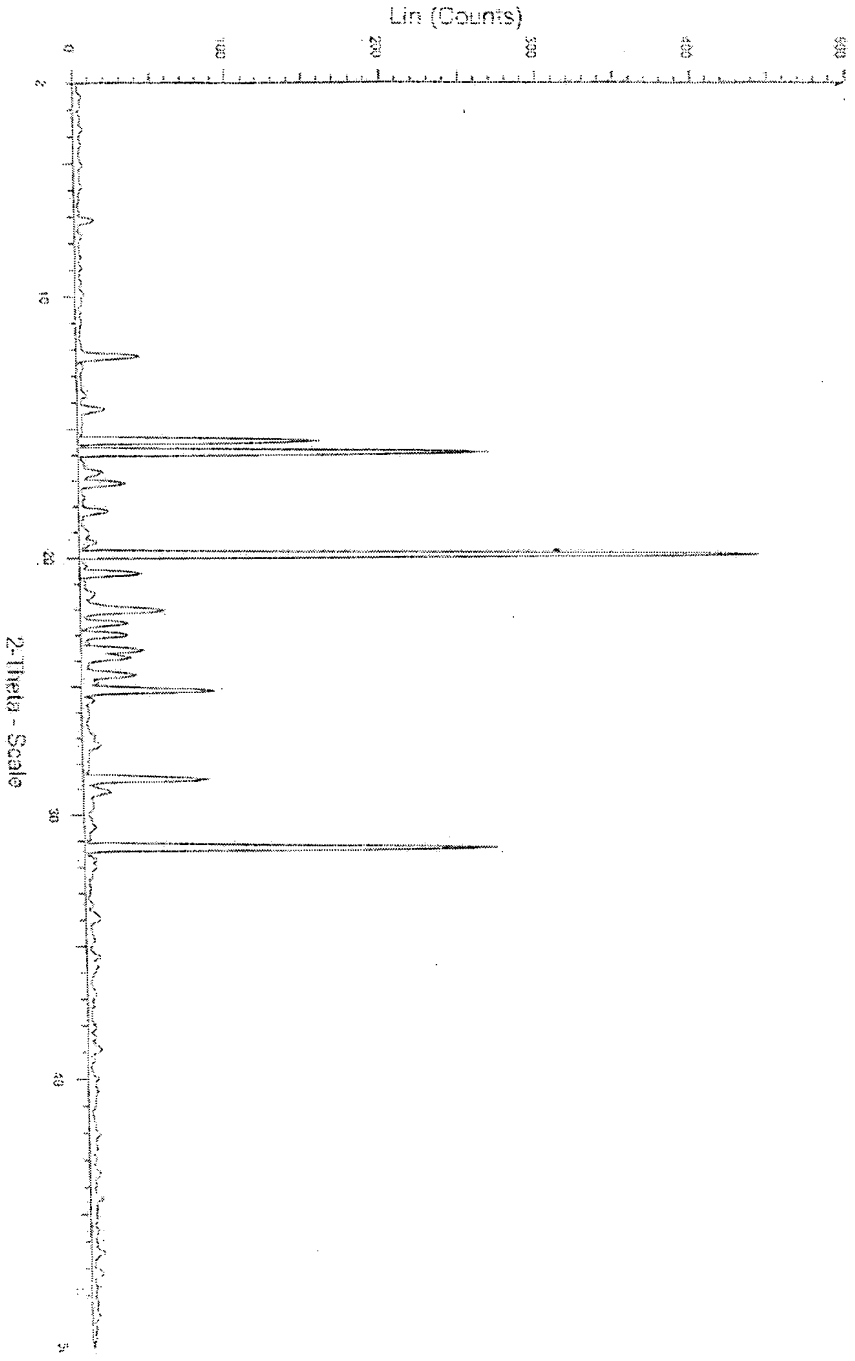
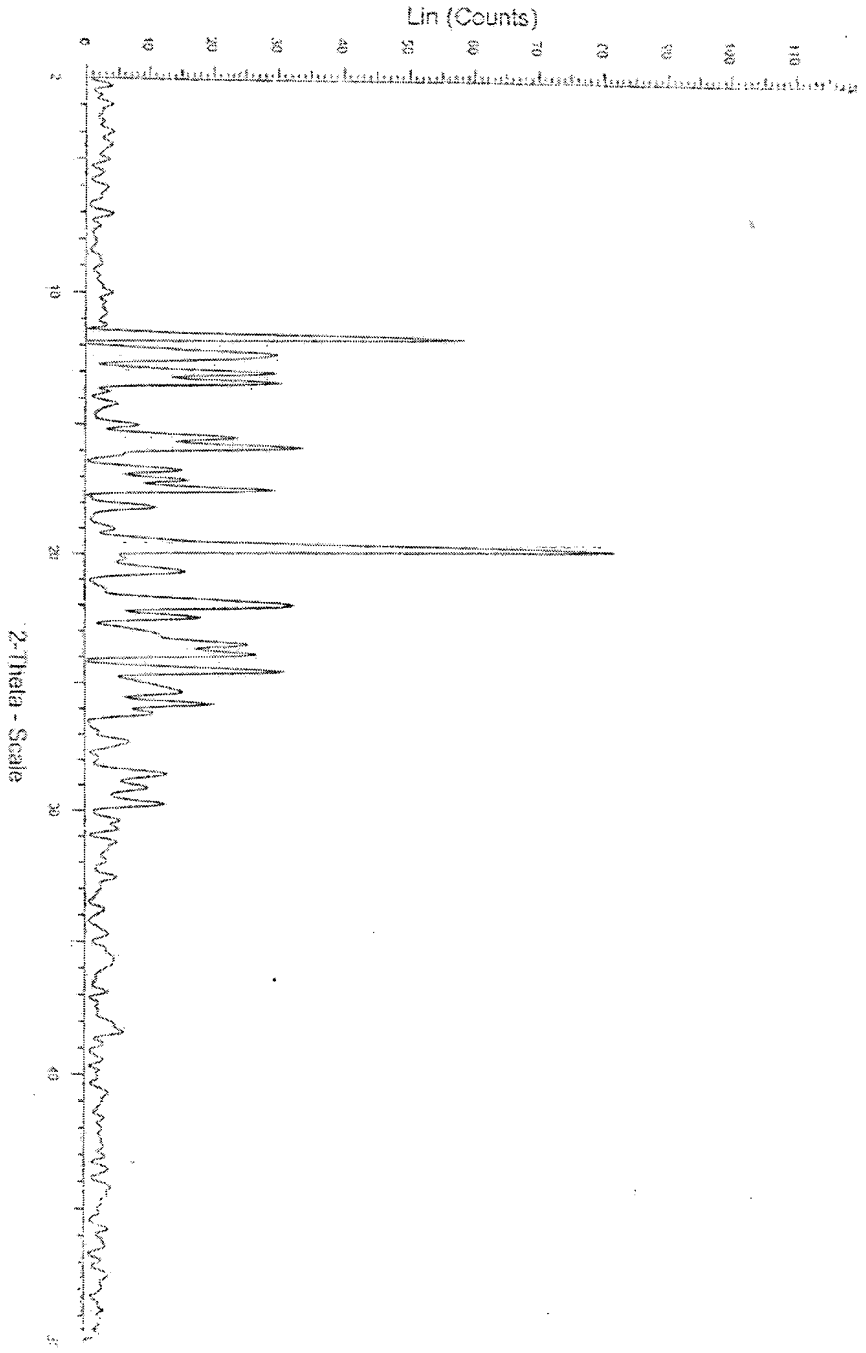


fig. 3/3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00139-0

CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 261/16; A61K 31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPOQUE, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5633272 A (TALLEY) 27 May 1997 (27.05.97) *column 23, lines 59-64; claims 1-28.*	1,3-6,8-10,12-17
A	US 5859257 A (TALLEY) 12 January 1999 (12.01.99) *column 33, line 25 - column 34, line 27; claims 3,4.*	1,3-6,8-10,12-17

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 December 2003 (04.12.2003)	21 January 2004 (21.01.2004)
Name and mailing adress of the ISA/AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. 1/53424/535	Authorized officer KOLLER G. Telephone No. 1/53424/458

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN 03/00139-0

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 2,7,11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 2, 7 and 11 refer to figures of the drawing and contravene Rule 6.2(a) PCT.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IN 03/00139-0

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
US A 5633272		DE	I	10399017I	2003-09-18
		CN	A	1442139	2003-09-17
		PL	B	185544B	2003-05-30
		LU	A	91024	2003-08-04
		ZA	A	9601150	1997-02-12
		DE	T	69623444T	2003-06-05
US A 5859257		DE	I	10399017I	2003-09-18
		CN	A	1442139	2003-09-17
		PL	B	185544B	2003-05-30
		LU	A	91024	2003-08-04
		ZA	A	9601150	1997-02-12
		DE	T	69623444T	2003-06-05